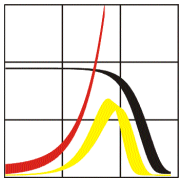

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Hamilton's Indicators of the Force of Selection

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Abstract

Hamilton (1) quantified the force of selection on an age-specific mutation. Hamilton's indicators of the age-specific force of selection always decline with age. This result is of profound importance to the theory of the evolution of senescence (2,3). Here I derive alternative indicators within Hamilton's framework. These indicators are as plausible and valid as Hamilton's and in some circumstances and over some age ranges they increase with age.

How does a mutation that only acts at a specific age a influence the evolutionary success of an individual? Does it matter if this age is early or late in life? These questions inspired Hamilton's (1) article in 1966 on the moulding of senescence. Hamilton built on the insight of Medawar (4) that later acting genes should be under weaker selection than earlier acting ones due to the unavoidable decline in the number of survivors at higher and higher ages. A genetically-determined fatal disease that only struck at post-reproductive ages would be entirely out of reach of the force of selection.

Hamilton pondered how to quantify the age-specific force of selection by considering the effect of a mutation on fitness. The bigger the change in fitness caused by a mutation the stronger should be the force of selection for or against it.

Hamilton used the most widely-accepted measure of Darwinian fitness, the intrinsic rate of population increase r, implicitly defined by the discrete version of the Lotka equation

$$\sum_{x=0}^{\infty} e^{-r\,x}\, l_x\, m_x \;=\; 1. \tag{1}$$

The function l_x gives the chance of survival to age x. The function m_x gives the amount of reproduction at that age. If the population is stable, as assumed by Hamilton, then each combination of an age-specific maternity function m_x and an age-specific survival function l_x is associated with exactly one real r that satisfies Eq. 1. The survival function l_x is defined as the product of the probabilities p_a of survival from age a to $a+1$:

$$l_x \;=\; p_0\, p_1\, \ldots\, p_{x-1}, \tag{2}$$

with

$$l_0 \;=\; 1.$$

The age-specific survival probabilities p_a depend on the instantaneous death rate μ_t, the force of mortality between age a and $a+1$, via

$$p_a \;=\; e^{-\int_a^{a+1} \mu_t\, dt} \;=\; e^{-\bar{\mu}_a}. \tag{3}$$

The cumulated mortality in the exponent reflects the average mortality during that time interval, denoted by $\bar{\mu}_a$.

By taking the derivative of Eq. 1 with respect to $\ln p_a$ and rearranging, Hamilton derived his basic result:

$$H^\dagger \equiv \frac{d\,r}{d\,\ln(p_a)} = \frac{\sum_{x=a+1}^{\infty} e^{-r\,x}\,l_x\,m_x}{\sum_{x=0}^{\infty} x\,e^{-r\,x}\,l_x\,m_x}. \tag{4}$$

The value of $H^\dagger$ is a measure of the force of selection. It captures the change in fitness r induced by an increase in $\ln p_a$. An increase in $\ln p_a$ is equivalent to a reduction in average mortality between age a and $a+1$, as shown in Eq. 3. This sensitivity of fitness to changes in age-specific survival is captured by the ratio of remaining reproduction, the numerator of Eq. 4, to generation time, the denominator. Because $H^\dagger$ declines as age increases, Hamilton (1) concluded that the force of selection must decline with age.

Alternative Indicators

It is puzzling that Hamilton did not calculate dr/dp_a, dr/dq_a, $dr/d\ln q_a$ or $dr/d\ln(\bar{\mu}_a)$, where q_a is the probability of dying and $\bar{\mu}_a$, as noted above, equals $-\ln p_a$. The results are as follows:

$$\frac{d\,r}{d\,p_a} = \frac{1}{p_a}\,H^\dagger, \tag{5a}$$

$$\frac{d\,r}{d\,q_a} = -\frac{1}{p_a}\,H^\dagger, \tag{5b}$$

$$\frac{d\,r}{d\,\ln(q_a)} = -\frac{q_a}{p_a}\,H^\dagger \tag{5c}$$

and

$$\frac{d\,r}{d\,\ln(\bar{\mu}_a)} = -\,\bar{\mu}_a\,H^\dagger. \tag{5d}$$

Strikingly, the expressions in Eq. 5a-d can increase in absolute value with age in contrast to $H^\dagger$, which always declines.

Consider, for instance, Eq. 5d. At pre-reproductive ages the value of $dr/d\ln\bar{\mu}_a$ is entirely determined by $\bar{\mu}_a$, as $H^\dagger$ is constant before maturity. At reproductive ages the change in

fitness with respect to mortality increases from age a to $a+1$ if

$$\left|\frac{d\,r}{d\,\bar{\mu}_a}\right| < \left|\frac{d\,r}{d\,\bar{\mu}_{a+1}}\right|.$$

Using the notion of reproductive value, introduced by Fisher (5),

$$v_a = \frac{e^{r\,a}}{l_a}\,\sum_{x=a}^{\infty}\,e^{-r\,x}\,l_x\,m_x, \tag{6}$$

this inequality can be rearranged to give the following condition,

$$\left(\frac{\bar{\mu}_{a+1}\,-\,\bar{\mu}_a}{\bar{\mu}_{a+1}}\right)\frac{v_{a+1}}{m_{a+1}}\,>\,1. \tag{7}$$

Hence, the value of $dr/d\ln\bar{\mu}_a$ will increase with age if $\bar{\mu}_a < \bar{\mu}_{a+1}$ and if future reproductive value is sufficiently large compared to fertility m_{a+1}. Taking into account the fact that Eq. 1 must hold, the inequality in Eq. 7 can be rearranged as

$$m_{a+1} < \left(\frac{\bar{\mu}_{a+1}\,-\,\bar{\mu}_a}{\bar{\mu}_{a+1}}\right)\frac{e^{r\,(a+1)}}{l_{a+1}}\left(1\,-\,\sum_{x=0}^{a}\,e^{-r\,x}\,l_x\,m_x\,\right). \tag{8}$$

This inequality determines trajectories for m_{a+1} that lead to increasing sensitivity of fitness to changes in mortality over age given a specified, increasing path for $\bar{\mu}_a$.

Fig. 1 and Fig. 2 provide an illustrative example. If age-specific survival probabilities p_a

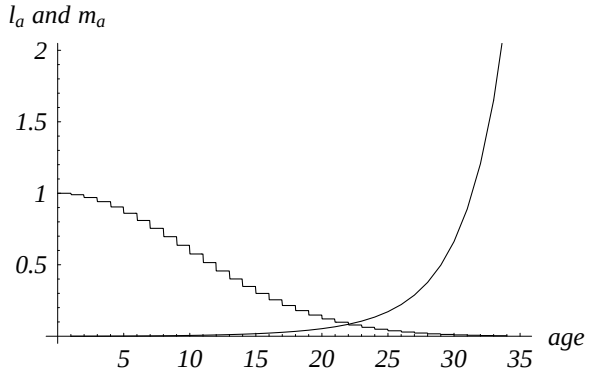

Figure 1: Example of survival and maternity function l_a and m_a.

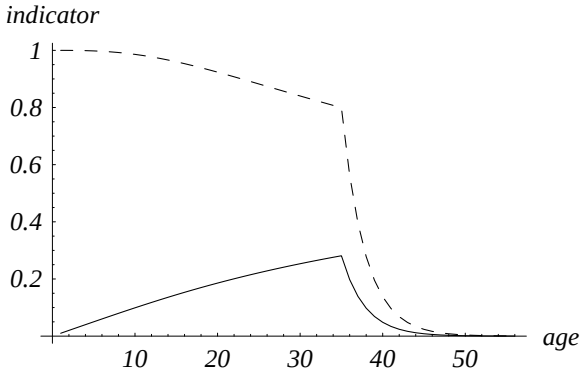

Figure 2: Comparison of $H^{\dagger} = \frac{dr}{d \ln p_a}$ (dashed line) with $\frac{dr}{d \ln \bar{\mu}_a}$ (solid line)

change according to

$$p_a = C\,(p_0)^a, \tag{9}$$

with $p_0 < 1$, then the average mortality between age a and $a+1$ is given by

$$\bar{\mu}_a = -\ln\left(C\,(p_0)^a\right) = -[\ln C + a \ln p_0]. \tag{10}$$

Choosing each m_{a+1} to be 0.01 units smaller than the right hand side of the inequality in Eq. 8 and setting $r = 0$, $C = 1$, $p_0 = 0.99$ and $m_0 = 0$, the resulting plot for survival and fertility for ages where the inequality in Eq. 7 holds can be seen in Fig. 1. By age 34 survival falls to 0.25%. After age 34 I fixed age-specific survival p_a at its level of $p_{35} = 0.70$ corresponding to $\bar{\mu}_{35} = 0.35$ and adjusted m_a to a constant level of 133.265 such that Eq. 1 is fulfilled. The indicators $dr/d\ln\bar{\mu}_a$ and $dr/d\ln p_a$ are plotted in Fig. 2. While Hamilton's indicator $H^{\dagger}$ declines, the alternative one increases until age 34. The increase would have continued if m_{a+1} was further determined by the inequality in Eq. 8. This, however, would result in a trajectory for m_a that would rise to enormous heights.

The quantity Hamilton derived for the force of selection on age-specific mutations that affect fertility is

$$H^* \equiv \frac{d\,r}{d\,m_a} = \frac{e^{-r\,a}\,l_a}{\sum_{x=0}^{\infty} x\,e^{-r\,x}\,l_x\,m_x}. \tag{11}$$

Hamilton considered survival effects on a log scale: He could have done the same for repro-

Table 1: Various indicators of the force of selection in Hamilton's framework

Indicator	Change with age a
$\frac{d\,r}{d\,\ln p_a}$	$-$
$\frac{d\,r}{d\,p_a}$	$+$ or $-^*$
$\frac{d\,r}{d\,q_a}$	$+$ or $-$
$\frac{d\,r}{d\,\ln q_a}$	$+$ or $-$
$\frac{d\,r}{d\,\ln(\bar{\mu}_a)}$	$+$ or $-$
$\frac{d\,r}{d\,m_a}$	$-$
$\frac{d\,r}{d\,\ln m_a}$	$+$ or $-$

* The change with age can be positive or negative depending on the trajectories of m_x and l_x.

duction, calculating

$$\frac{d\,r}{d\,\ln(m_a)} \;=\; m_a\,H^*. \tag{12}$$

Hamilton's indicator in Eq. 11 necessarily declines with age but the alternative indicator in Eq. 12 can increase with age depending on the trajectory of m_a.

Table 1 summarizes the direction of changes over age of the various indicators of the force of selection. The differences in the dynamics are due to the nonlinear transformation of p_a to $\ln p_a$ and m_a to $\ln m_a$.

Are Some Indicators Better?

Most evolutionary-demographic modelling, including Lee's (3) recent extension of Hamilton's results, is done within a continuous framework using the Lotka equation

$$\int_0^\infty e^{-r\,x}\,l(x)\,m(x)\,dx \;=\; 1. \tag{13}$$

As Hamilton noted, the indicators $H^\dagger$ and H^* can be equivalently formulated in continuous time. Lee (3) worked with the continuous versions of $H^\dagger$ and H^*. Alternatively he could have used the indicators $\bar{\mu}H^\dagger$ in Eq. 5d and mH^* in Eq. 12 which can similarly be used in

continuous time. The indicators in Eq. 5a-c apply to a discrete framework.

Charlesworth (2, p.191), who reconstructed Hamilton's results, suggested that "genetic effects on survival probabilities are more likely to be additive on a log scale." His conjecture implies that mutations have additive effects on mortality. Indeed, both of Hamilton's indicators $H^{\dagger} = dr/d\bar{\mu}$ and $H^{*} = dr/dm$ can be interpreted as assuming that mutations additively affect average mortality $\bar{\mu}$ and fertility m. This is plausible because additive risk factor models are widely used in demographic and epidemiological research. Even more widely used are proportional-hazard models. The indicators $\bar{\mu}H^{\dagger}$ and mH^{*} capture the effect of a proportional change in $\bar{\mu}$ and m.

Whether age-specific mutations act proportionally or additively is a question for empirical research. Most demographic and epidemiological analyses of risk factors have found that proportional effects are more common than additive effects. In particular, the impact of genetic polymorphisms, such as ApoE 2, 3 and 4, on mortality are captured by proportional hazards (6). Hence, it seems plausible that the indicators $\bar{\mu}H^{\dagger}$ and mH^{*} will prove at least as valid as Hamilton's indicators.

Hamilton's Narrow Road

Let me now briefly review the weaknesses of all the indicators in Table 1. None of the indicators can explain the declining age-trajectories of mortality during development. Whereas Hamilton's indicator $H^{\dagger}$ predicts a constant force of selection associated with a constant mortality schedule before the age of first reproduction, the alternative indicators Eq. 5a-d are determined by the current level of age-specific survival. High pressure at mortality peaks and low pressure at mortality valleys would tend to smooth a mortality trajectory. Perhaps such smoothing has occurred, but mortality trajectories are far from flat at pre-reproductive ages. Mortality trajectories generally decline steeply during development (3,7).

All the indicators in Table 1 imply that the force of selection drops to zero when reproduction ceases. Several authors have argued that lethal mutations should accumulate, yielding a black hole of death at the age when reproduction ends (8-12). However, various species

enjoy a period of post reproductive life. Mortality trajectories at higher ages level off and sometimes decline for humans, Medflies, *Drosophila* and the nematode worm *C.elegans* (7). It should be noted that as the force of selection peters out, genetic drift is the only force that determines the fate of a gene. Research is needed on the extent to which genetic drift will lead to an accumulation of mutations at post-reproductive ages (Steven Orzack, personal communication).

Hamilton's approach also suffers from other deficiencies (13). Important factors such as trade-offs, intergenerational transfers, changing environments and gene–gene and gene–environment interactions are not incorporated. Eq. 1 requires the strong assumption of a one-sex stable population. Age-specific mutations might be unusual. To the extent they occur most such mutations may affect a range of ages. Hence, the quantities in Table 1 are, at best, indicators and not measures of the force of selection. None provides more than a rough impression about the direction and magnitude of the force of selection on survival and reproduction.

Conclusion

Hamilton's approach does not explain the shape of the age-trajectories of mortality and fertility during development and during the post-reproductive lifespan, two of the three periods of life. Furthermore his approach has other severe weaknesses, some of which Hamilton recognized. Nonetheless, Hamilton concluded that the force of selection inevitably has to decline with age, even "in the farthest reaches of almost any bizarre universe" (14). This conclusion has been generally accepted. Hamilton's universal claim can be disproved, however, even adopting his restrictive assumptions. As shown above, alternative indicators can be derived, within Hamilton's own framework, that can result, in some circumstances and over some age ranges, in an increasing force of selection with age.

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